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An Explorative Qualitative Analysis of Participants' Experience of using Kava versus Placebo in an RCT

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Running header: The Experience of Taking Kava in an RCT

Abstract

Background: Many randomized controlled trials have been conducted using *Piper methysticum* (Kava); however no qualitative research exploring the experience of taking Kava during a clinical trial has previously been reported.

Patients and Methods: A qualitative research component (in the form of semi-structured and open-ended written questions) was incorporated into an RCT, to explore the experiences of those participating in a clinical trial of Kava. The written questions were provided to participants at Weeks 2 and 3 (after randomization, after each controlled phase). The researcher and participants were blinded as to whether they were taking Kava or placebo. Two open-ended questions were posed to elucidate their experiences from taking either Kava or placebo. Thematic analysis was undertaken and researcher triangulation employed to ensure analytical rigour.

Results: Key themes after the Kava phases were a reduction in anxiety and stress, and calming or relaxing mental effects. Other themes related to improvement in sleep and in somatic anxiety symptoms. Kava use did not cause any serious adverse reactions, although a few respondents reported nausea or other gastrointestinal side-effects. This represents the first documented qualitative investigation of the experience of taking Kava during a clinical trial. The primary themes involved anxiolytic and calming effects, with only a minor theme reflecting side-effects.

Conclusions: Our exploratory qualitative data was consistent with the significant quantitative results revealed in the study, and provide additional support to suggest the trial results did not exclude any important positive or negative effects (at least as experienced by the trial participants).

Introduction

Piper methysticum (Kava) has been used for millennia by Pacific Island cultures for recreational, cultural and medicinal purposes [1]. Many randomized controlled trials have been conducted using this phytotherapy for the treatment of generalized anxiety, with meta-analyses revealing significant efficacy against placebo [2]. However, no previous qualitative research has reported on the experience of taking Kava during a clinical trial.

Qualitative research to explore people's experience of using herbal medicine is still in its infancy. Qualitative measures may form the focus of a study, or be part of a 'mixed-methods' approach whereby a qualitative component augments the quantitative mainstay of a randomized controlled trial [3-5]. These measures can assist in understanding how participants experience the intervention, which can help in developing hypotheses for future research, and may identify previously unknown therapeutic benefits or side-effects. We therefore incorporated a qualitative research component into a recent trial [6].

The Kava Anxiety Depression Spectrum Study (KADSS) was a 3-week randomized, placebo-controlled, double-blind, crossover trial on Kava, in a patient group with elevated anxiety. Participants (*n*=60) were adults (18-65 years) reporting at least one month of persistent worry or anxiety. They were recruited between April and October 2008. Each placebo-controlled phase of the trial lasted one week. Interventions comprised 5 tablets per day of Kava (each containing 3.2g, standardized to 50mg of kavalactones) or placebo. The prescription comprised 2 tablets in the morning and afternoon, and one in the evening (providing a total of 250mg kavalactones in active treatment: the maximum dose approved in Australia). Kava tablets were supplied by MediHerb Pty Ltd (Warwick, Australia), and assessments were administered by the lead author at the Royal Brisbane and Women's Hospital (RBWH) in Brisbane, Australia during May-October 2008. The clinical trial met the standards of the Declaration of Helsinki, and was approved by The University of Queensland's Medical Research Ethics Committee (Project number 2008000340), and registered on the Australian and New Zealand Clinical Trial Register (ACTRN12608000536369).

The quantitative results of KADSS revealed a highly significant reduction of participant's anxiety and depression compared to placebo [6]. Qualitative data collection to explore the participant's experience of taking Kava was also undertaken with a view to providing a richer understanding of: (A) Kava's psychophysical benefits, and (B) salient and common adverse effects, including any that had not previously been reported.

Patients and Methods

In addition to quantitative measures, a semi-structured and open question written form was provided to all 41 consenting and randomized participants. Responses from the end of both Phase I and II of the crossover trial were available from 28 participants: these data were used for analysis. As the trial was double-blind and placebo-controlled, both the researcher and participant were blinded to condition when qualitative fieldwork was undertaken.

Qualitative data collection employed written questions with participants providing written responses. A pilot form was initially constructed via a consensus between

researchers, before being tested on a sample of colleagues for feedback on the utility of its format. The form was then slightly modified to address the feedback.
The questions were as follows:

1) "Please describe any positive effects that occurred during the week you believe occurred from taking the tablets"
2) "Please describe any negative effects that occurred during the week you believe occurred from taking the tablets"
3) "Did any external changes occur this week"? YES -please describe/NO.

These questions were administered at the Mental Health Centre, Royal Brisbane and Women's Hospital in Brisbane Australia during mid-late 2008. They were completed after the first and second controlled phases of the crossover trial, providing responses from participants taking either Kava or placebo. A researcher from the University of Queensland administered the forms, initially explaining the procedure, and informed the participants that they had as long as they required in completing the written question forms. The researcher left the room and participants completed provided written responses in privacy. Participants were asked to provide as much detail as possible. On completion the participants returned their written responses in a sealed envelope.

A thematic approach, in broad relation to the three areas/questions introduced, was used to analyse the qualitative data. Three main themes were developed a) Positive experiences from taking Kava b) Negative experiences from taking Kava c) Experiences of taking placebo. Researcher triangulation (whereby individual researchers provided independent readings of the written responses, with any divergences of interpretation discussed until resolution is reached) was undertaken to help strengthen the rigour of the analysis produced.

Results

A total of 28 participants from the trial provided qualitative data (see Table 1 for characteristics). As detailed in Table 2, data was coded into six primary domains. These domains were decided by consensus between the authors after review of the transcripts. Domains involved participants' positive experiences of taking Kava (on anxiety or mood, sleep or somatic symptoms) and negative experiences thought to have occurred during a Kava phase. The final area explored participants' experiences of being on placebo and examined any differences between this and the Kava phase. Examples of participants' experiences are detailed below. Statements that best represent the main themes are provided. As a result, some participants' responses are not included, while others are quoted multiple times.

---------- Insert table 1 about here----------

.....Insert table 2 about here.....

Relief of Stress and Anxiety from Kava

In response to the question posed to participants about any positive effects, the vast majority of participants reported positive experiences in the week they took Kava.

Participants explained that they experienced a reduction of perceived stress or anxiety, an elevation in mood, improvement in sleep pattern, and a reduction of somatic symptoms of stress. Calming or relaxing mental effects were commonly reported:

> "I have been more relaxed in the past week... and I am able to cope a lot easier. My usual anxiety symptoms have decreased or disappeared" (participant no. 55)

> "I have been able to handle stress in a more positive light...mind has 'stopped ticking' so late in the evening" (participant no. 59)

> "Found it easy to accomplish day to day activities without getting worked up...I had a pretty hectic week but didn't feel too concerned or nervous about anything" (participant no. 18)

> "Felt more calm than usual, especially in the evening. Not as fearful of the worst happening" (participant no. 52)

Reports by a small number of participant's of Kava being beneficial in the 'evening' was an interesting finding, given that this may refer to improvements in sleep (see also below), as insomnia is endemic in anxiety [7].

Effects of Kava on Mood

Participants also reported elevated mood during the Kava phase. It was unclear from the responses whether the elevation of mood was an independent effect, or was a consequence of the reduction of anxiety.

> "My mood was significantly up from last week" (participant no. 26)

> "Feel happier about things" (participant no. 54)

> "Achieved much more, completed tasks would have normally put off...Elevated mood 4 out of 6 days, general elevated feeling of wellness" (participant no. 07)

> "Improved mood" (participant no. 21)

> "This week my overall sense of wellbeing has improved" (participant no. 20)

In contrast, some participants reported that their depression remained the same or even worsened during this phase. Whether this was a consequence of Kava consumption or a fluctuation in their mood due to other causes is unknown. Why Kava may enhance some people's mood and not others is also unclear.

> "New low mood, slightly depressed mood...feeling pessimistic and 'down', negative thoughts and outlook, low motivation. No change in worrying and 'mental' anxiety, easily stressed" (participant no. 31)

> "Feel slightly depressed this week- feel negative about future" (participant no. 29)

> "Not as positive as previous week...socially a bit withdrawn...Had a major stress out with kids- did not deal with it well" (participant no. 21)

> "Negative experiences still remain- inability to concentrate, depressive symptoms, feelings of frustration, lack of motivation, degree of anxiety" (participant no. 36) (Also stated that this was not new- just continuing from previous weeks).

Effect of Kava on Sleep

Another theme emerging from the analysis of some participants' open responses was a positive effect of Kava on their sleep. This may have reflected a hypnotic effect of Kava, or be a supplementary effect of feeling less anxious and stressed. As a number of participants' reported:

> "Sleep is improved, sleeping through the night without waking frequently... Falling asleep earlier which is rare- mind has stopped ticking so late in the evening" (participant no. 59)

> "Felt more calm... for example I fell asleep in front of TV, and I rarely do that" (participant no. 52)

Other participants stated that sleep was less of an issue for them and that their overall sleep time was increased when they were taking Kava.

> "Sleeping a bit longer now, 6-7 hours instead of 5" (participant no. 54)

> "Sleeping better...insomnia less of a problem" (participant no. 13)

Kava's Effect on Physical Signs of Anxiety

A further theme identified from the analysis involved positive physical consequences, including an experience of reduction of muscular or physical tension.

> "A marked reduction in physical tension... Palpitations, tightness in my chest ceased completely" (participant no. 1)

> "Less neck tension and muscular aches...no headaches...butterflies reduced" (participant no. 13)

> "Muscles especially through my arms and hands felt relaxed and less wound up...physical calmness was apparent" (participant no. 52)

> "Lower grade physical symptoms... and no physical sensations e.g. no racing heart, hyperventilation, tingling, numbness... Feeling less flushed or feeling hot or faint, and no 'wobbly' feeling... No stomach symptoms- less stomach upset or indigestion...better digestive health with no constipation" (participant no. 31)

Physiological Side Effects possibly from Kava

Several participants reported experiencing mild negative physical reactions that occurred during a Kava phase. An adverse reaction noted by four participants involved minor gastrointestinal side effects after starting the Kava tablets. The effect was mild, and only one person dropped out due to nausea. In the latter case, the nausea commenced at the start of the Kava week and abated shortly after cessation of the tablets (no qualitative data was available for this participant).

> "Slight pain in middle upper abdomen" (participant no. 18)

> "Stomach upset on second day (not first)... Also felt a bit of nausea on the 3rd day" (participant no. 52)

> "Stomach cramps and nausea experienced at the beginning of the tablets- may be related to cycle" (participant no. 59)

Some participants described how they felt tired or fatigued during the Kava phase. Interestingly, both participants commented that their tiredness was evident during the day.

> "Feeling tired really easily...fatigued often and early during the day...Very little stamina...Mild headaches" (participant no.31: This participant also had positive changes in somatic symptoms—see above).

> "I've felt tired or more tired than I would normally- particularly in the middle of the day" (participant no. 32)

Other effects were described in isolation by single participants. They included tinnitus, sensitivity to light, and tightness of the chest. In all cases these symptoms were experienced during the initial placebo period and carried into the controlled phases. An unusual effect reported by a female participant was of a hangover after drinking wine: she said she would not normally experience this. In summary, no major adverse effects or reactions emerged from our thematic analysis providing exploratory support for the trial finding that Kava was well tolerated by this sample.

Effect of Being on Placebo compared to Kava

Reviewing the reported experiences of participants receiving placebo provides insights regarding the contrast to the responses of those receiving Kava. A theme of negative moods or of intense suffering emerged during the placebo phase. The most common negative effects concerned a continuing experience of anxiety, stress, nervousness or fear.

> "No noticeable effects on anxiety and stress...quite bad, in fact a little worse than usual" (participant no. 1)

> "...My stress and anxiety stayed elevated, still poor concentration, and motivation...feeling of nervousness in general" (participant no. 18)

> "No positive effect occurred- Felt quite fearful and anxious" (participant no. 52)

> "Very apprehensive, not a good feeling, free floating anxiety like first week of trial (placebo week)...haven't felt that restless before" (participant no. 13)

Interestingly, in the placebo week that followed the Kava week, some participants commented that the week was 'not as good' as the previous week. As indicated by the participants' descriptions below, this may in some cases have constituted 'withdrawal'. However, others (e.g. participant no. 54), still reported feeling better than before starting the trial.

> "Felt as though things were wearing off...Had moments of feeling anxiety coming but could remember how I felt the week before and took some deep breathes which eased it...felt in control...While I had a return of some feelings of anxiety and symptoms, still feel a lot better than week 1 of the programme and before " (participant no. 54)

> "Felt like the way people have described to me what occurs when coming off antidepressants" (participant no. 13)

> "Not coping as well as the previous week" (participant no. 36)

Several people reported a positive week during a placebo phase, and some were certain they were on Kava during the placebo week. Furthermore, some participants thought they were improving week by week. Comments such as 'this week feels like a higher step' by participant no. 37, could indicate an erroneous belief that they were on Kava, a natural course of remission of their disorder, or a carryover effect from the previous week taking the herbal medicine.

> "Improved sleep, more relaxed, calmer, lower stress levels, improved mood" (participant no. 19)

> "Last week felt good, but this week feels like a higher step" (participant no. 19)

> "If what I believe is correct and I am on the real thing there didn't seem to be a comedown or hangover or residual effect" (participant no. 37)

> "Finding it more easy to control stress...find it easy to come down or change behaviour...no 'impending doom' feelings of nervousness" (participant no. 31)

Discussion

Results of the exploratory qualitative component of KADSS were both consistent with and expanded upon the significant quantitative results of Kava on the Hamilton Anxiety Scale, Montgomery-Asberg Depression Rating Scale, and the Beck Anxiety Inventory (cf. Sarris et al. [4]). Many respondents to our qualitative research component suggest they had experienced positive effect while taking Kava three times a day for one week. The reported positive effects on stress, anxiety or mood are consistent with the highly significant reductions on quantitative depression and anxiety outcome measures that were revealed in the study. Positive themes uncovered from participant's experience of

Kava included a lessening of anxiety, an enhancement of mood, improvement in sleep, and some beneficial effects on somatic symptoms of anxiety. However, some people detailed many positive experiences from Kava while concurrently also describing negative experiences. Participants' experiences during a placebo week were equally as mixed, with many people still documenting positive effects from the tablets.

A specific theme that was identified from the analysis included an experience of reduction of muscular or physical tension. This makes sense, as Kava has previously been observed to have antispasmodic properties via GABAergic activity in part from ion channel modulation [8]. Some participants described how they felt tired or fatigued during the Kava phase. Kava is known to have somatically sedating properties, and these sensations do appear consistent with the consequences of the biological down-regulation of arousal pathways [8].

While Kava is often seen as a treatment specifically for anxiety, positive supplementary effects occurring from reducing stress and anxiety should not be underestimated. Some participants explained that their sleeping had improved. Sleep dysregulation is a common symptom of depression and anxiety, and the effect of insomnia on daytime functioning and overall health is substantial [9]. Although not explored in this clinical trial, reduction of anxiety and stress may also affect many other health areas (e.g. reducing high blood pressure, improving digestion, and reducing risk of depression [10].

The only themes that were revealed in respect of side effects concerned gastrointestinal symptoms and tiredness. Four participants experienced mild gastrointestinal symptoms (one dropping out with nausea). Gastrointestinal side effects such as nausea are a known negative effect from Kava, and is in part due to the kavalactone "dihydromethysticin" [11]. A few participants reported feeling more tired, although others said they felt more energized and motivated during the Kava phase. Interestingly, while the pooled data on the MADRS revealed a significant reduction on depression, some participants noted that their mood worsened during the Kava phase. This result highlights the complexity and uniqueness of the individual's experience of medicinal interventions, and how individual experiences may not always be reflected in average data.

Limitations of the qualitative component of KADSS are acknowledged. The use of a written semi-structured assessment form does not provide the rich exploration of experience that can achieved from interviews with open-ended questions or focus groups, and the small sample size meant that only very common effects of kava could be reliably detected. Nevertheless, the qualitative data presented here does provide the first exploration of this important topic and should prompt further, more in-depth investigation of participants' experiences as part of herbal medicine trials. A further limitation concerns the use of a short treatment period and a cross-over design without a washout phase. This means that participant's long term experience of Kava cannot be assessed from this trial, and that some carryover effect from the first active phase may have occurred.

The placebo effect is common, especially in clinical trials testing psychiatric interventions [12]. What is of note, is that these placebo effects experienced in this study were still occurring even after a quarter of participants who were "placebo-responders" were removed from the trial (participants with response of >50% reduction of anxiety score on anxiety scales during an initial "placebo run-in" week).

Qualitative research is still in its infancy in the arena of herbal medicine clinical trials. In KADSS we found that utilizing a qualitative assessment component in the study provided a valuable addition to the quantitative data. Overall the exploratory experiential data provided by the participants was found to reflect the general findings of the quantitative trial data, in as much as it supports an interpretation that an aqueous extract of Kava has a beneficial effect on reducing most participants' anxiety and depressive symptoms. In respect to potential negative experience from Kava, our exploratory data tentatively suggests (within this small sample) that the plant medicine is safe at this dosage and for this short period of time.

Conflicts of Interest

None noted

Funding

No direct funding was received. The University of Queensland supplied clinic space for the trial. MediHerb supplied the Kava tablets used in the study.

Key Points

- Exploratory qualitative data tentatively suggested that participants' experiences may provide evidence of positive effects on anxiety, stress and mood
- A small number of participants reported nausea or other gastrointestinal upsets
- No new adverse reactions were identified
- Results were consistent with Kava having beneficial effects and being well tolerated

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Table 1. Baseline characteristics of participants who were later randomized to groups

Categorical variables	Placebo/Kava n /14 (%)	Kava/Placebo n /14 (%)
Male	7 (50%)	7 (50%)
Employed/studying	12 (86%)	13 (93%)
CIDI-Auto Diagnosis		
Social Phobia	3 (21%)	8 (57%)
Panic Disorder	6 (43%)	4 (29%)
Generalized Anxiety Disorder	8 (57%)	10 (71%)
Major Depressive Disorder	3 (21%)	4 (29%)
Dysthymia	0 (0%)	2 (14%)
Depression (previous diagnosis)	0 (0%)	6 (43%)
Continuous variables	**Placebo/Kava Mean (SD)**	**Kava/Placebo Mean (SD)**
Age (yr)	44.4 (13.1)	43.1 (11.7)
Education, y	11.7 (2.3)	12.7 (3.1)

Table 2. Key themes identified

Major domains
Relief of Stress and Anxiety from Kava
Effects of Kava on Mood
Effect of Kava on Sleep
Kava's Effect on Physical Signs of Anxiety
Physiological Side Effects possibly from Kava
Effect of Being on Placebo compared to Kava